

Advanced Parental Age at Birth Is Associated With Poorer Social Functioning in Adolescent Males: Shedding Light on a Core Symptom of Schizophrenia and Autism

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Background: Evidence indicates an association between older parents at birth and increased risk for schizophrenia and autism. Patients with schizophrenia and autism and their first-degree relatives have impaired social functioning; hence, impaired social functioning is probably an intermediate phenotype of the illness. This study tested the hypothesis that advanced father's age at birth would be associated with poorer social functioning in the general population. To test this hypothesis, we examined the association between parental age at birth and the social functioning of their adolescent male offspring in a population-based study. **Methods:** Subjects were 403 486, 16- to 17-year-old Israeli-born male adolescents assessed by the Israeli Draft Board. The effect of parental age on social functioning was assessed in analyses controlling for cognitive functioning, the other parent's age, parental socioeconomic status, birth order, and year of draft board assessment. **Results:** Compared with offspring of parents aged 25–29 years, the prevalence of poor social functioning was increased both in offspring of fathers younger than 20 years (odds ratio [OR] 1.27, 95% confidence interval [CI] 1.08–1.49) and in offspring of fathers 45 years old (OR 1.52, 95% CI 1.43–1.61). Male adolescent children of mothers aged 40 years and above were 1.15 (95% CI 1.07–1.24) times more likely to have poor social functioning. **Conclusions:** These modest associations between parental age and poor social functioning in the general population parallel the associations between parental age and risk for schizophrenia and autism and suggest that the risk pathways between advanced parental age and schizophrenia and autism

might, at least partially, include mildly deleterious effects on social functioning.

Key words: schizophrenia/social functioning/parental age

Introduction

Advanced father's age at birth has been associated with increased risk of schizophrenia^{1–7} and autism.^{8–10} Advanced mother's age at birth has also been associated with schizophrenia^{5,11} and autism,¹⁰ but the evidence is less consistent. It is hypothesized that schizophrenia and autism are diseases affected by multiple genes and environmental factors,¹² but these factors can also contribute to the manifestation of other mental disorders or intermediate phenotypes such as poor cognitive or social functioning. It is further hypothesized that the deleterious effects of the risk factors are manifested as mental illness only when individuals cross a certain severity threshold.¹³ Hence, advanced parental age might not be a risk factor for a specific mental disorder such as schizophrenia or autism but rather increases risk for brain malfunction that rarely crosses the threshold for a clinical diagnosis. Certain degrees of social impairment are not uncommon in mental illness in general, and are essential for the diagnosis of schizophrenia and autism.¹⁴ The present study therefore aimed to examine the hypothesis that advanced parental age at birth is associated with decreased social abilities, reflected by decreased social functioning, across the entire range of social functioning levels in the general population. To this end, we analyzed data on parental age and social functioning from the assessments performed by the Israeli military on all adolescent males in the country.

Methods

The Israeli Draft Board Registry includes cognitive and behavioral data on all 16- to 17-year-old Israeli males. The draft board assessment includes a semistructured interview assessing demographics (including parental age at birth), personality, and behavioral traits, including social functioning. College-aged individuals have to complete 4

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Table 1. IQ and Socioeconomic Status (SES) Levels in Male Adolescents With Poor Vs Normal-High Social Functioning

	Low Social Functioning			Normal-High Social Functioning			<i>P</i>
	Minimum	Maximum	Mean (SD)	Minimum	Maximum	Mean (SD)	
IQ	70	130	95 (15)	70	130	100 (14)	<.01
SES	1	20	11.29 (4.1)	2	20	12.21 (4.0)	<.01

months of training to qualify to administer the semistructured interview. The interview scale includes questions such as How many good friends do you have? Do you have a girl friend? Do you generally prefer to be with or without a group of companions? How often do you go out on Friday evenings? Do you tend to be the center of the party? Scale points are (1) very poor—complete withdrawal, (2) poor—weak interpersonal contacts, (3) adequate—can form relationship with individuals and in a group, (4) good—good interpersonal relationships, and (5) exceptional—superior interpersonal relatedness. The test-retest reliability of the behavioral assessment for inductees interviewed after several days by different interviewers is above 0.8, and population-based norms are available for each of the tests.^{15,16}

For purposes of this study, the total score of social functioning was used. The median for the social functioning score is 3, the mean score is 3.04, with an SD of 0.72, and 25.6% of the adolescent males assessed received a score of 1–2. Because the behavioral assessment is not administered to adolescent females, only adolescent males were included in the current analysis.

This study was approved by the local institutional review board.

Study Population

Of 438 486 Israeli-born male adolescents consecutively screened by the Israeli Draft, 96.9% had valid data on parental age at birth. We excluded 4.7% who had missing or incomplete data on the medical, including psychiatric, assessment, and 8.8% who had missing data for social functioning. The final analytic sample included, therefore, 403 565 Israeli-born male adolescents.

Statistical Analyses

For purposes of analysis, social functioning was treated as dichotomous variable, comparing those male adolescents with very poor or poor social functioning (1–2 on the original scale) with those with adequate, good, or superior social functioning (3–5 on the original scale). Father's age at birth was treated as a categorical variable, divided into 7 age categories: younger than 20 years, 20–24 years, 25–29 years (considered to be the reference category), 30–34 years, 35–39 years, 40–44 years, and 45 years of age and above.¹⁷ Mother's age at birth was similarly defined in 6 levels: younger than 20 years, 20–24

years, 25–29 years (considered to be the reference category), 30–34 years, 35–39 years, 40 years and above.

Birth order, proband's IQ, the other parent's age at time of birth, and socioeconomic status significantly affected social functioning scores in this dataset (table 1 and 2); hence, they were added as covariates in the analyses, all treated as continuous measures. Due to slight variations in the draft board scoring of social functioning over the years, we also included the year of the draft board assessment as a covariate. Separate analyses were performed for father's and mother's age at birth (defined categorically as mentioned above).

Logistic regression was used to calculate the association between parental age and social functioning, yielding odds ratios (ORs) and 95% confidence intervals (CIs), both before and after adjustment for potential confounders.

Multicollinearity was tested using Pearson correlation and collinearity diagnostics provided by the multiple regression procedure, including variance inflation factors—VIF—and tolerances. Analyses were conducted using SPSS 15.0.

Results

Father's Age

Unadjusted analyses showed an “U-shaped” pattern: male adolescent children of fathers younger than 20 years at birth had increased prevalence of poor social functioning scores (OR = 1.72, 95% CI = 1.49–1.98); male adolescent children of fathers belonging to the oldest age group (≥ 45 years) were 1.71 (95% CI = 1.63–1.79) times more likely to have poor social functioning compared with male adolescent children of fathers aged 25–29 years at birth. These results were slightly attenuated but remained significant after controlling for potential confounders (table 3).

Mother's Age

Similar to father's age, unadjusted analyses of the association between mother's age and social functioning also showed an “U-shaped” pattern: male adolescent children of mothers younger than 20 years at birth had increased prevalence of poor social functioning scores (OR = 1.21, 95% CI = 1.16–1.27), and male adolescent children of mothers belonging to the oldest age group (≥ 40 years)

Table 2. Distribution of Male Adolescents With Poor Vs Normal-High Social Functioning and Birth Order

Social Functioning Category	Birth Order				<i>P</i>
	1 st (%)	2 nd (%)	3 rd (%)	4 ⁺ (%)	
Low	40.9	31.4	17.3	10.3	<.01
Normal-high	39.3	33.6	18.6	8.5	

were 1.61 (95% CI = 1.52–1.71) times more likely to have poor social functioning compared with male adolescent children of mothers aged 25–29 years at birth. This U-shape distribution was lost when possible confounders were entered into the analysis; male adolescent children of mothers belonging to the oldest age group (≥ 40 years) were 1.15 (95% CI = 1.07–1.24) times more likely to have poor social functioning compared with male adolescent children of mothers aged 25–29 years at birth (table 3).

Collinearity

Pearson correlation indicated that father's age at birth was highly correlated with mother's age at birth ($r = 0.79$). Correlations between birth order, IQ, and father's age were all $r \leq 0.5$. The highest variance inflation factors (VIF) score was 2.41 and the lowest tolerance score was 0.4 therefore collinearity scores are within accepted ranges of multicollinearity.^{18,19}

Discussion

This population-based study found an “U-shaped” relationship between social functioning and father's age at

birth, with male adolescent children of both younger and older fathers having increased prevalence of poor social functioning. The increase in prevalence of poor social functioning in offspring of younger fathers parallels some of the evidence regarding father's age and risk for schizophrenia; one article¹⁷ reported increased risk of schizophrenia in children of younger fathers, with other articles^{3,4} reporting trends in the same direction. Increased risk for schizophrenia in children of older fathers is a well-replicated finding,^{1–7} and increased risk for schizophrenia in children of older mothers has also been reported in previous studies.^{5,11} Advanced father's age has also been shown to increase risk for autism,^{8–10} an illness also characterized by impaired social functioning.

Impaired premorbid social functioning is strongly associated with later schizophrenia,²⁰ and unaffected siblings of patients with schizophrenia²¹ and with autism²² have impaired social abilities that are intermediate between their affected brothers and population norms. Thus, poor social functioning might represent a behavioral expression of familial, perhaps increased, genetic risk. It is conceivable that at least part of the effect of increasing parental age on risk for schizophrenia and autism is mediated by the relationship between increasing parental age and poor social functioning. The biological mechanism by which advanced father's age affects social functioning is not known. It is conceivable that the same mechanisms evoked to explain the association between increased father's age at birth with schizophrenia are relevant here. One explanation is that there is a higher frequency of point mutations in males, the frequency of which increases with age.²³ Other forms of mutation, such as altered copy number in repeat DNA, and chromosome breakage have also been related to male

Table 3. Association Between Father's and Mother's Age at Birth and Social Functioning in Male Adolescents

Parental Age at Birth (y)	Normal-High Social Functioning (%) (<i>N</i> = 299 559)	Low Social Functioning (%) (<i>N</i> = 68 685)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Fathers				
Less than 20	0.2	0.4	1.72 (1.49–1.98)	1.27 (1.08–1.49)
20–24	12.3	11.9	1.05 (1.02–1.08)	0.93 (0.9–0.96)
25–29	37.4	34.5	1	1
30–34	27.4	25.9	1.03 (1.01–1.05)	1.07 (1.05–1.1)
35–39	14.0	15.4	1.2 (1.17–1.23)	1.21 (1.17–1.25)
40–44	6.1	7.8	1.39 (1.34–1.43)	1.31 (1.25–1.37)
≥ 45	2.6	4.1	1.71 (1.63–1.79)	1.52 (1.43–1.61)
Mothers				
Less than 20	3.5	4.0	1.21 (1.16–1.27)	0.9 (0.85–0.95)
20–24	30.9	29.5	1.0 (0.98–1.03)	0.91 (0.9–0.96)
25–29	36.1	34.3	1	1
30–34	20.2	20.4	1.06 (1.04–1.09)	1.06 (1.03–1.09)
35–39	7.8	9.4	1.27 (1.23–1.31)	1.12 (1.07–1.16)
≥ 40	1.6	2.4	1.61 (1.52–1.71)	1.15 (1.07–1.24)

^aAdjusted analyses controlled for cognitive functioning, the other parent's age, parental socioeconomic status, birth order, and draft board year of assessment. OR, odds ratio; CI, confidence interval.

aging.^{24,25} In addition, advancing age is associated with dysregulation of epigenetic processes.²⁶

The finding of poor social functioning in offspring of very young fathers may also be related to their elevated risk of de novo genetic disorders, which may result from immaturity of spermatids or from low activity of DNA repair or antioxidant enzymes.²⁷

The association between advanced mother's age and poorer social functioning might involve nucleotide repeat instability.²⁸ Trinucleotide or triplet repeats are 3 nucleotides consecutively repeated within a region of DNA and have been found to undergo a type of genetic mutation, termed a "dynamic" or "expansion mutation." In this type of mutation, through mechanisms that occur during DNA replication and are only partially understood, the number of triplets in a repeat increases.²⁹ Unlike repeats of normal length, in which length changes only rarely from one generation to the next, expanded repeats tend to be unstable and will typically become longer over successive generations. Trinucleotide repeats are more common in offspring of older, compared with younger, women.²⁸ During the past decade, nearly 20 diseases caused by a trinucleotide repeat expansion have been identified, as well as other diseases caused by related mutations, including schizophrenia, autism, Huntington disease, and fragile X syndrome.^{30,31}

This study's results are consistent with similar findings indicating that advanced paternal age at birth is related to other medical conditions and complex behavioral phenomena in offspring³² such as Apert syndrome,³³ Down syndrome,³⁴ achondroplasia,³⁵ newborn death,³⁶ birth weight,³⁷ diabetes,³⁸ and intelligence.³⁹

Social functioning can be affected by many causes, which might or might not be relevant for schizophrenia. On one hand, impaired social functioning is certainly a core symptom of patients with schizophrenia, and in large historical prospective study, impairment on this measure of social functioning was a strong predictor of later schizophrenia (OR = 4), a much larger effect than, for instance, low IQ.²⁰ Also, siblings of schizophrenia patients have social functioning scores slightly below those of normal controls.²¹ On the other hand, there are many possible sources of impaired social functioning, both in schizophrenia and in adolescents without a diagnosable mental illness. One person might be suspicious and afraid people want to hurt him, another desperately wants social contact but is afraid of rejection, another might have less need for social interactions, another might want social interactions but lack the appropriate social skills to do so, etc. The data available here do not enable us to parcel out these possibilities. Hence, although there are good reasons to assume that the decrease in social functioning caused by advanced parental age at birth in the population is related to schizophrenia, there are probably other reasons not related to schizophrenia that play a role in impaired social functioning as well.

These results are limited in that social functioning is assessed only in males, and we cannot know what effect, if any, increased paternal age has on social functioning in females. This is particularly significant during adolescence because gender-based differences in social functioning are not unlikely at these ages. Regarding schizophrenia, at least 2 of the articles published on the topic of paternal age and schizophrenia^{2,5} reported that advanced father's age at birth was associated with increased risk for later schizophrenia both in male and female offspring; hence, it would be reasonable to assume that advanced parental age would be a poor social functioning in females as well.

In summary, social functioning is worse in sons of very young and of older parents. This effect is relatively small (OR = 1.5) and is probably not clinically relevant. The significance of this finding is conceptual, in that it implies that very young and advanced parental age might increase risk for schizophrenia via a slightly deleterious effect on social functioning. This finding is consistent with a similar finding of advanced parental age having a slightly deleterious effect on cognitive abilities.³⁹ Taken together, these data further our understanding of risk for schizophrenia, indicating that the risk pathway of advanced parental age on schizophrenia might, at least partially, work via its mildly deleterious effects on social functioning and cognition.

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